Australasian Neuromuscular Network

Welcome to the Australasian Neuromuscular Network (ANN)

We are very excited to bring you the first ANN newsletter.

The neuromuscular community within Australia and New Zealand has a very positive history of research collaboration, and over the past few years there has been increasing discussion about the need for an integrated diagnostic and clinical network. A recent conference held in Sydney provided an opportunity for action, and the ANN was formed.

The ANN is committed to establishing a cohesive, integrated neuromuscular network that enables people to work together across Australia and New Zealand for the well-being of patients. We will provide a forum to advance and disseminate information, be a single voice to advocate for patients and guide best practice in diagnosis, care and treatment.

The ANN is structured to address issues relating to clinical care and research effort. Each area has a Steering Committee comprising individuals with expertise in each area, as well as providing representation of all major groups active in the care and study of individuals with neuromuscular disorders across Australia and New Zealand.

The ANN has also joined the European neuromuscular network as a partner of TREAT-NMD, and is closely affiliated with US consortia - allowing us to gain from and contribute to a global effort.

The ANN extends an invitation to join to anyone involved in caring for those affected by neuromuscular disorders - membership is free.

Members will benefit from ready access to Standards of Care, standardised proformas, unified approach to ethical approvals and consent, improved communication through regular e-newsletters and a dedicated website, notification of opportunities to participate in registries, research studies and clinical trials, opportunities to establish special interest groups, training opportunities and advice and provision of expertise to establish multi-disciplinary services.

Please feel free to contact relevant Steering Committee Chairs if you would like to raise or discuss a particular issue.

INSIDE

Steering Committees

Clinical Care
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Advocacy/Funding Opportunities
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Deb Robins (Qld); Andrew Kornberg (Vic); Nigel Laing (WA); Kathryn North (NSW); Hilary Rayner (NZ); Julie Cini (Vic); Varlli Beetham (Vic)

What we aim to do

Clinical Care
- Communicate effectively via Clinical Care Network
- Map expertise in each state
- Circulate Standards of Care guidelines
- Liaise with ANZ Child Neurology, AAN, HGSA, Neuropathology

Research
- Circulate information relating to research collaborative studies
- Develop a database for collection of research data
- Identify opportunities for collaborative studies

Diagnostic
- Make Standard of Care guidelines readily available
- Circulate specimen collection and clinical checklist for use in development of guidelines
- Develop standardised consent forms/ information sheets
- Establish a model for improved coordination between research and diagnostic laboratories
- Establish guidelines for incorporation of pathology and molecular/genetic screening in diagnostic labs
- Determine list of genes being tested and location
- Determine the most appropriate model to enable a coordinated nationwide diagnostic service

Clinical Trials
- Coordinate training of local evaluators/coordinators
- Circulate information concerning new trials
- Identify opportunities for collaborative studies

Fundraising
- Identify opportunities for fundraising for infrastructure to support ANN
- Identify opportunities for Government support
- Develop financial model to distribute funds raised jointly

Standards of Care

Diagnosis and management of DMD

Although guidelines are available for various aspects of DMD, comprehensive clinical care recommendations do not exist. This year, for the first time, Kate Bushy and colleagues published a comprehensive two-part article in Lancet giving recommendations on best practice in the management of Duchenne muscular dystrophy. The Lancet articles are available to download from the TREAT-NMD website over the next few weeks at http://www.treat-nmd.eu/patients/DMD/dmd-care/ and then the article can be accessed at http://www.treat-nmd.eu/dmd-care in the following weeks on the new TREAT-NMD website.

The article provides pivotal guidance for anyone involved in the care of patients affected by DMD. It is particularly important for those caring for patients who do not have access to a range of specialists, as "input from different specialties and the emphasis of interventions will change as the disease progresses".

The article is also a very useful tool to assist with the diagnosis of DMD, physiotherapy, surgery, neuromuscular and skeletal assessments and management, pharmacological interventions and psychosocial, pain, respiratory, cardiac and nutritional management.

The article has also been translated into a 'family-friendly' version and is also available on the TREAT-NMD website over the next few weeks at http://www.treat-nmd.eu/patients/DMD/dmd-guide-languages/ and can then be accessed at http://www.treat-nmd.eu/dmd-guide-languages.

Diagnosis and management of SMA

The International Standard of Care Committee for Spinal Muscular Atrophy was formed in 2005, with a goal of establishing practice guidelines for clinical care of these patients. Consensus was achieved in 2007 on several topics related to common medical problems in spinal muscular atrophy, diagnostic strategies, recommendations for assessment and monitoring, and therapeutic interventions in each care area. The Consensus Statement for Standard of Care in Spinal Muscular Atrophy and a user friendly version are both available to download for the next few weeks from http://www.treat-nmd.eu/patients/SMA/sma-care/ and can then be accessed at http://www.treat-nmd.eu/sma-care.

Diagnosis and management of FSHD

A report has been published on standards of care and clinical trial readiness for facioscapulohumeral muscular dystrophy (FSHD). The report is based on the outcomes of a European Neuromuscular Centre (ENMC) workshop held in the Netherlands in January of this year. FSHD is the third most common muscle disorder and although no definite cure exists, careful management of the symptoms can lead to significant improvements in quality of life. The report was published in Neuromuscular Disorders [20(7):471-5].

Best Practice

Best Practice Guidelines on Molecular Diagnostics for Duchenne/ Becker muscular dystrophies

Following a meeting of senior scientists from Australia, Europe, USA and India in The Netherlands in November 2008, a consensus Best Practice Guidelines for molecular diagnosis of Duchenne and Becker muscular dystrophy has also been published in Neuromuscular Disorders [20(6):422-427] and can be freely downloaded from http://download.journals.elsevierhealth.com/pdfs/journals/0960-8966/PIIS0960896610001860.pdf

The guidelines recommend the appropriate tests that are to be carried out, interpretation of the results and how those results should be reported.

Australian Duchenne Muscular Dystrophy Registry

The availability of health information via the internet has become a critical resource for clinicians, researchers and affected families. Parents and advocacy groups have also become increasingly aware of international registries that provide opportunities for children to access new therapies through clinical trials. In Australia, Duchenne muscular dystrophy (DMD) advocacy groups led by the Duchenne Foundation Australia, in conjunction with the state Muscular Dystrophy Associations, the Muscular Dystrophy Foundation, other support groups and affected families, made representations to state and federal politicians and health ministers to establish a national registry. Their relentless campaigning led to the development of the very first Australian National DMD Registry to collate clinical and genetic information. The establishment of the Registry was made possible by the inter-jurisdictional cooperation of the state clinical and genetic testing services across the country with coordination and key support from Dr Hugh Dawkins and the Office of Population Health Genomics, Department of Health WA.

The Australian Duchenne Muscular Dystrophy Registry provides an opportunity for Australian DMD patients to participate in clinical trials being undertaken anywhere in the world. The Registry is linked directly to the TREAT-NMD global network of registries, an international effort which has proven effective in improving the health and management of boys with DMD. The Registry provides an important enabling tool for clinicians and clinical trial sponsors to quickly identify patients suitable for each study, particularly those therapeutic strategies that target specific genetic defects.

Potential Benefits of a DMD Registry

- Centralise information and provide an interface between patients, doctors and researchers
- Coordination of diagnosis, therapy and prevention - universally available across Australia
- Promote sense of community and belonging among affected patients and families and provide ready access to information concerning standards of care, research and available therapies
- Monitor and benchmark data to improve health care performance across institutions and providers
- Promote baseline standards of care available to all patients and families - provision of the "right care at the right time"
- Provide essential information necessary to leverage government and industrial support for further infrastructure

The database is open to anyone affected by DMD and is entirely voluntary – data obtained is held securely and confidentially. Most of the clinical and genetic information about each patient will be entered locally by the patient's primary physician in association with the genetic testing laboratories in each state.

We are in the process of getting ethics approvals for the registry. Patient information will be de-identified in any central/international data collections - so that only clinical and genetic data is made available. Potentially eligible patients will be informed about new trials and studies through their primary physicians.

The DMD registry will be launched nationally on 15th November.
Please visit the website: https://www.nmdregistry.com.au/dmd/
Further information will be available in our next newsletter.

A web-based Myotonic Dystrophy registry collecting data to allow compatibility with the TREAT-NMD and USA University of Rochester registries is also being developed and we hope will be available by April 2011.

With other registries including Spinal Muscular Atrophy to follow!

Specimen Collection Procedures Manual:

State Neuropathology Service

(University of Melbourne)

Many of us can relate to receiving poor quality tissue, and this was one issue that is key to improving diagnosis for neuromuscular disorders. As part of a working party to develop guidelines for improved diagnosis, Paul Kennedy, Senior Scientific Officer at the State Neuropathology Service, has circulated a detailed set of collection guidelines - these will be available shortly on the ANN website.

The guidelines outline how to prepare biopsy kits to provide to clinical staff, how to send the specimens, how to process the specimens, how to freeze tissue - critical pathways to ensuring that the tissue is of the highest quality for diagnosis.

Upcoming events

Australian Health and Medical Research Congress
14th - 19th November 2010
Melbourne, Australia

181st ENMC workshop on ongoing updating and dissemination of standards of care for DMD
10th - 12th December 2010

4th UK Neuromuscular Translational Research Conference
29th - 30th March 2011
London, UK

63rd American Academy of Neurology Annual Meeting
9th - 16th April 2011
Honolulu, Hawaii

Myology Congress
9th - 13th May 2011
Lille, France

16th World Muscle Society Congress
18th - 22nd October 2011
Algarve, Portugal

TREAT-NMD Global Conference
8th - 11th November 2011
Geneva, Switzerland

Adult Pompe Disease

Successful treatment of infantile Pompe's disease (Acid maltase deficiency, alpha-glucosidase deficiency, Glycogenosis type 2) with alpha-glucosidase infusion has increased interest in the adult onset form. To date there has not been conclusive evidence for the effectiveness of alpha-glucosidase in late onset patients and it has not yet been approved for this indication in Australia.

Pompe disease is said to have an incidence of about 1:40,000 – 50,000 live births but may be significantly more frequent. The adult onset variant can be difficult to diagnose because of insidious onset and relatively normal muscle biopsy. I have recently seen two (2) new cases that had not been diagnosed appropriately after routine muscle biopsy histochemical staining had been reported as normal. The characteristic features of

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muscle fibre cytoplasmic lysosomal vacuoles staining for acid phosphatase and increased glycogen may not be seen.

Electron microscopy will show increased glycogen in the cytoplasm and autophagic vacuoles but is not done routinely. The clinical presentation is with early onset shortness of breath and particularly orthopnea due to diaphragmatic weakness associated with predominantly proximal lower limb weakness.

There is prominent paraspinal wasting and complex repetitive EMG discharges in paraspinal muscles. There will be a significant difference between standing and lying FEV1.

The adult variant may come on from the 2nd to the 6th decade and the diagnosis is often delayed. The diagnosis can be made on careful review of the muscle biopsy and confirmed by measurement of alpha-glucosidase activity on a dried blood spot. This assay is performed in the National Reference Laboratory (Department of Biochemical Genetics, 4th floor Rogerson Building, 72 King William Road, North Adelaide, SA 5008, phone 08 81617249).

Adult Pompe disease should be included in the differential diagnosis of limb girdle muscular dystrophy especially when associated with dyspnoea.

Prof Alastair Corbett

Trial News

Australian sites participates in international Exon 51 trial

Exon skipping continues to show great promise as a treatment strategy for Duchenne muscular dystrophy. Exon skipping is a strategy in which molecules called antisense oligonucleotides target error-containing parts of a gene and coax cells to retain the error-free parts for protein synthesis - by 'skipping' the gene the production of dystrophin can be returned.

As part of an international consortium and in partnership with GlaxoSmithKline, Australian sites will participate in the trial of PR0051 for ambulatory and non-ambulatory boys with mutation correctable by skipping exon 51.
!2 boys participated in an earlier smaller study conducted overseas, and most showed improvement in the 6 minute walking test. Recruitment of eligible patients is underway in Sydney and Melbourne for the Phase III trial.

Through a partnership between Prosensa and GlaxoSmithKline, clinical trials will in the future be extended to include an additional four (4) exons - 45, 52, 53 and 55. Preliminary studies are currently underway to examine the safety and efficacy of PR044 that targets exon 44.

AVI BioPharma has also developed an exon skipping strategy and results from clinical trials conducted by the MDEX consortium (involving Steve Wilton, Katie Bushby and Francesco Muntoni) have reported generation of new dystrophin-positive muscle fibres amongst patients. Future clinical trials are planned to optimise the dosing regime.

Genzyme continues to work with PTC on Ataluren

In April, following the completion of the international trial, Dr Brenda Wong (study investigator) presented additional data that demonstrates that those on the lower dose of Ataluren did better on the 6 minute walking test than the high dose or placebo. While the 6 minute walking test was the primary endpoint, additional endpoints included changes in muscle function, muscle strength and dystrophin expression - PTC Therapeutics are currently working to complete their analysis.

Action Duchenne posted an update on their website in June to advise their community that Genzyme is working closely with PTC to completely understand the results of the ongoing additional analyses. Once PTC and Genzyme have clearer insight on the best path forward globally, they will come back to the community with an update. PTC and Genzyme are aware of the need for a treatment for nonsense mutation Duchenne and Becker muscular dystrophy, and will continue to partner to investigate various options that may help bring a safe and effective therapy to the community.

What is a Clinical Trial?

Clinical trials are the interface between research and therapy. Clinical trials are an important step prior to introducing new discoveries and new treatments into clinical practice in a safe and controlled way - so that we are continually gathering evidence for what really works..and what doesn't..to improve the current standard of care.

Participation in a clinical trial is a very important personal decision and one that often involves the family to make that decision. Patients and families are provided with comprehensive information that allows them to make an informed decision. Agreeing to participate in a trial is not binding, participants are free to leave the study at any time. There is a rigorous peer review process involved in designing and running a clinical trial. An assessment of the scientific validity, ethical implications, potential adverse effects and the information provided to parents is undertaken by Scientific Review and Ethics Committees.

There is a huge national effort underway to assess promising new therapies for Duchenne muscular dystrophy (DMD). It may surprise you to learn that while steroids have been the mainstay of treatment for DMD for many years, there has never been a properly designed and performed clinical trial to work out the best timing and dose.

In recent years, access to international patient registries have provided Australian patients with opportunities to participate in international clinical trials.

In the 1970'S the leukemia survival rate was 25%
In 2009 the survival rate was 92%
This increase was the result of clinical trials.

A recent trial of Ataluren (PTC124), aimed at improving muscle function, was successfully undertaken by Australian sites and recruitment is currently underway for an exon skipping trial.

Accurate diagnosis and local expertise and resources to run clinical trials as part of an international effort is critical. Coordinated national patient registries that feed into global registries are also playing an increasingly important role - for rare disorders like DMD, a global effort ensures the increased likelihood of a trial proceeding and also ensures that all suitable patients can be identified.

Towards a Brighter Future - February 2010

270 carers, parents, members of the community, clinicians, allied health professionals and researchers attended the Towards a Brighter Future Conference in Sydney, February 26th-27th.

The conference attracted 61 highly regarded speakers from around the world and across a broad range of areas - there was unanimous agreement that the quality of the program was excellent.

Of the 77 attendees who responded to the post-conference evaluation, 40% were parents, approximately half of the delegates were from NSW and QLD, DMD was the neuromuscular disorder of greatest interest, and the vast majority of attendees came to hear the latest research and clinical trial news.

Overall, attendees reported that the high points of the conference included the opportunity to network, hearing young people speak, the quality of the speakers (and inspirational speakers) and research/clinical trials updates.

TOWARDS A BRIGHTER FUTURE
Sydney 2010

The Congenital Muscular Dystrophy International Registry

The Congenital Muscular Dystrophy International Registry (CMDIR) was created to identify the global CMD population for the purpose of raising awareness, standards of care, clinical trials and in the future a treatment or cure.

The CMDIR is a patient self report registry, launched in September 2009, now available in French, German, Spanish and English, with Turkish, Danish, Italian, Japanese and Portuguese pending.

The registry includes demographic, disease specific and diagnostic questions. The CMDIR has online help and genetic counselors available to answer questions. If patients do not yet have genetic confirmation of disease, CMDIR counselors will help find a laboratory to determine the genetic mutation (if known).

CMD Subtypes included in CMDIR:

- Ullrich CMD
- Merosin deficient
- CMD, undiagnosed (including merosin positive)
- Dystroglycanopathy (WWS, MEB, Fukuyama)
- Integrin alpha 7 deficiency
- Integrin alpha 9 deficiency
- Laminopathy (Lamin A/C)
- SEPN 1related myopathies: SEPN (selenoprotein deficiency) and RYR 1(ryanodine receptor)

LGMD subtypes included in CMDIR:

- Bethlem myopathy
- Dystroglycanopathies (LGMD2K, LGMD2I, LGMD2L, LGMD2N)

The CMDIR's goal is to register the global CMD population, both those with and without genetic confirmation and to provide a centralised resource for the posting of CMD- LGMD clinical studies and trials. The CMDIR registers across the CMD to LGMD spectrum for the "CMD" genes with the knowledge that therapeutic development may not differentiate between age of onset.

The CMDIR is neither a natural history study nor a genotype-phenotype database - it exists as a patient/family resource with the ability to contact eligible patients regarding active and recruiting CMD clinical studies and trials with no obligation to participate.

CMDIR oversight is provided by the CMDIR Advisory Board.

For more information about CMDIR please visit www.cmdir.org

Communication

We aim to circulate regular newsletters to all our members and we are currently developing a website resource.

If you know of clinicians or researchers who would be interested in reading this newsletter please feel free to send the newsletter to them. Membership is free and is open to anyone who is involved in or interested in neuromuscular disorders.

We have a new email address: info@ann.org.au - if you have information that is relevant to ANN members you are welcome to email us!